Malaria elimination: surveillance and response

Daniel J. Bridges¹, Anna M. Winters¹, Davidson H. Hamer^{2,3,4,5}

¹Akros Research Lusaka, Zambia, ²Zambia Centre for Applied Health Research and Development, Lusaka, Zambia, ³Center for Global Health and Development, Boston University, Boston, MA, USA, ⁴Department of International Health, Boston University School of Public Health, Boston, MA, USA, ⁵Section of Infectious Diseases, Department of Medicine, Boston University School of Medicine, Boston, MA, USA

In the last decade, substantial progress has been made in reducing malaria-associated morbidity and mortality across the globe. Nevertheless, sustained malaria control is essential to continue this downward trend. In some countries, where aggressive malaria control has reduced malaria to a low burden level, elimination, either nationally or subnationally, is now the aim. As countries or areas with a low malaria burden move towards elimination, there is a transition away from programs of universal coverage towards a strategy of localized detection and response to individual malaria cases. To do so and succeed, it is imperative that a strong surveillance and response system is supported, that community cadres are trained to provide appropriate diagnostics and treatment, and that field diagnostics are further developed such that their sensitivity allows for the detection and subsequent treatment of malaria reservoirs in low prevalence environments. To be certain, there are big challenges on the road to elimination, notably the development of drug and insecticide resistance. Nevertheless, countries like Zambia are making great strides towards implementing systems that support malaria elimination in target areas. Continued development of new diagnostics and antimalarial therapies is needed to support progress in malaria control and elimination.

Keywords: Malaria, *Plasmodium falciparum*, Elimination, Sub-Saharan Africa, Zambia, Active case detection, Surveillance

Introduction

Substantial progress has been made in the last decade in reducing malaria-associated morbidity and mortality worldwide. In some endemic countries, aggressive malaria control has reduced the malaria burden to a point where malaria elimination is becoming a feasible reality either nationally or sub-nationally. In 2010, there were an estimated 216 million episodes of malaria with more than 80% occurring in sub-Saharan Africa.¹ Worldwide malaria mortality estimates for 2010 ranged from approximately 655 000 deaths to as high as 1 238 000,^{1,2} with the majority of these deaths occurring in children under 5 years old in the World Health Organization (WHO) African region. These figures represent a substantial decline in morbidity and mortality relative to the period from 1985 to 2005.² Between 2000 and 2010, malaria transmission also decreased by more than 50% in 43 of 99 countries reporting active transmission.¹ Thus, while morbidity and mortality due to malaria remain high in some areas, others have shown substantial

success in reducing parasite prevalence to levels where malaria elimination may now be feasible,³ a prospect that has re-invigorated the malaria community.

Major interventions contributing to the decline in malaria prevalence and mortality include the scaled up use of long-lasting insecticide-treated nets (LLIN), indoor residual spraying (IRS), widespread adoption and use of artemisinin-based combination therapy (ACT), improved diagnostics, and intermittent preventive treatment with sulfadoxine-pyrimethamine in pregnant women (IPTp). While these interventions have been highly successful in many countries, as outlined below, their utility is threatened by the development of insecticide resistance, ACT and sulfadoxine-pyrimethamine resistance, counterfeit drugs, and failure of health care workers to adhere to diagnostic test results.^{4–7} In addition, while there have been substantial amounts of funding provided in recent years for malaria control by the Global Fund, World Bank, the Bill and Melinda Gates Foundation, President's Malaria Initiative (PMI), and bilateral donors,⁸ concerns have been raised that there may not be sufficient resources to maintain high levels of coverage or to

Correspondence to: Davidson H. Hamer, MD Zambia Centre for Applied Health Research and Development 4649 Beit Road Lusaka, Zambia. Email: dhamer@bu.edu

attempt the more ambitious goal of eliminating malaria.⁹ With these concerns in mind, and recognizing that some countries have experienced reductions in malaria parasite prevalence such that elimination is becoming a realistic goal, new strategies are needed to achieve strong surveillance using in-country human resources and to provide targeted application of available interventions.

Malaria Elimination — Definitions, a Historical Perspective, and Success Stories

The definition of malaria elimination has progressed over the last five decades from reduction in transmission below a certain threshold to the current WHO definition.^{10,11} In the Malaria Elimination Field Manual for Low and Moderate Endemic Countries, elimination is defined as the ‘interruption of local mosquito-borne malaria transmission’. Countries that are able to maintain a malaria-free status for at least 3 years are eligible to be certified as malaria-free by the WHO.¹¹ In contrast, eradication describes the situation where malaria parasites have disappeared completely, worldwide.

There are many potential benefits that could arise from the elimination of malaria in a country or region, some of which are not easily quantified.¹² These include improved health of the local population; potentially longer life expectancy at birth; reduced total health expenditures; stronger systems for detecting, reporting, and responding to potential outbreaks and imported cases; national pride; cross-border collaborations; and indirect benefits such as greater educational attainment, agricultural productivity, and fertility.^{8,12}

The Global Malaria Eradication Program (GMEP), which ran from 1955 to 1969, did not succeed in its goal of eliminating malaria worldwide, but it did result in substantial decreases in the burden of malaria in many endemic countries. However, the campaign did not include countries in sub-Saharan Africa so it was not truly a global eradication campaign.¹² The GMEP relied primarily on the use of IRS with dichloro-diphenyl-trichloroethane (DDT) and active case detection and treatment.^{12,13} Due to its long residual effect which allowed applications only once or twice a year (in contrast to previously used pyrethrum extracts that required weekly applications), DDT became not only the insecticide of choice, but IRS with DDT formed the dominant intervention. The excessive reliance on IRS with DDT meant that other measures that had been used in the past for malaria control such as prevention of mosquito bites, drainage of mosquito breeding sites, and other forms of environmental control were no longer implemented in many locations. In addition, a belief that there was no

longer a need for additional knowledge to achieve malaria eradication meant that further research was deemed unnecessary.¹³

Despite the limited options available for malaria control during the GMEP, this campaign was able to reduce the number of countries and regions with malaria.¹² There were several positive contributions of the GMEP besides shrinking the malaria map. These included lessons learned on how to attain total coverage for a global health program, the development of stronger community-based volunteer cadres of health workers, use of local maps to guide malaria control activities, and improved quality of surveillance systems.^{13,14}

Unfortunately, the widespread use of DDT led to the emergence of vector resistance.¹⁵ Due to the high cost of the GMEP and recognition that malaria eradication was not a feasible outcome, UNICEF and other collaborating partners withdrew their support,¹³ and malaria began to rebound in many countries. This situation was further worsened by climatic conditions (a strong La Niña in 1975–1976), deforestation in Southeast Asian and Latin American countries¹³ (which increased human–mosquito contact), and antimalarial drug resistance, all of which contributed to the development of serious epidemics in the seventies.

In summary, the GMEP managed to reduce and even eliminate malaria from some countries, but in others it failed to control malaria. Nevertheless several important lessons were learnt that are essential to consider as we look again towards elimination.^{13,16,17} First, basic implementation and operational research are needed to support malaria control efforts. Second, high quality surveillance within public health systems is needed. Third, the vertical nature of the GMEP often resulted in a failure to incorporate malaria control activities into local health systems indicating that future efforts need to be carefully integrated into local health systems while accounting for socio-cultural context. Fourth, there is a need for active participation and understanding of communities in malaria control efforts. Finally, overdependence on only one or two major interventions (e.g. DDT, IRS, and case detection) should be avoided.

Malaria Control and Sustained Control

With this history in mind, and energized by a renewed vigor for malaria elimination fueled by the creation of the Millennium Development Goals, PMI, the Bill and Melinda Gates Foundation, and other participating key donors, the current Roll Back Malaria Global Malaria Action Plan (GMAP) lays out an aggressive three-part strategy to achieve malaria elimination and the eventual eradication of the disease.¹⁸ For

countries reporting moderate to high malaria prevalence, the strategy first calls for universal implementation of key malaria interventions (i.e. 100% intervention coverage for the population at risk with a target of at least 80% utilization). IRS, the distribution and use of LLINs, ACT, and IPTp are the available tools of choice. Even as countries achieve universal coverage, the risk for resurgence remains high unless part two of the GMAP is also achieved: sustained malaria control through health system support to deliver interventions such that high coverage continues.

Re-tooling for Elimination: Surveillance and Response are Key

As malaria control is sustained and transmission declines, the GMAP calls for malaria programs to enter a time of transition towards an elimination agenda. Depending on the intensity of transmission and vector capacity, programs of universal coverage should be augmented or even replaced by focalized detection with responses mounted for individual malaria cases. Such an elimination program should focus on completely interrupting endemic malaria transmission and preventing re-establishment.¹¹ In contrast to a control-focused program, an elimination program recognizes that residual transmission is heterogeneous¹⁹ allowing any remaining transmission foci to be identified and targeted for elimination. There is no agreed upon set of criteria that define whether an area is ready to embark on malaria elimination; however, Roll Back Malaria recommends when malaria incidence becomes less than 5 per 1000 people at risk or the slide positivity rate of all suspected malaria patients is less than 5%.¹⁸ Readiness for reorientation is judged on a country-by-country basis;¹² however, considering the financial, technical, political, and operational challenges, elimination is likely to only be successful by national 'shrinking the map' campaigns, i.e. application of elimination strategies in low-transmission zones within a country. For example, in Zambia, where the authors presently work, the current goal of malaria elimination is constrained to specific zones, with the hope that these efforts will work to enlarge these zones to eventually cover the entire country.²⁰ Irrespective of the national goals and strategies employed, interventions must be cost-effective and maximized for synergy with each other. Elimination is a goal that if pursued must be supported for the long term.

Surveillance within a control program may be considered purely a monitoring and evaluation tool, which measures whether interventions are achieving the desired reduction in specific indicators. Surveillance within the elimination stage,²¹ however, must be much more robust and sensitive with the

ability to detect, report, and respond to both symptomatic and asymptomatic malaria infections, both of which act as reservoirs for malaria parasite transmission.^{14,22,23} Surveillance systems must therefore be very precise with high enough sensitivity to detect individual infections within low prevalence areas. Furthermore, a surveillance system in an elimination environment must integrate with and inform responses. Thus, the collection of spatial locations of malaria cases is important in order to mount targeted responses. Timeliness of detection is another important aspect of surveillance²⁴ to enable a rapid response to be mounted for confirmed cases in order to target delivery of antimalarial medications, provision of LLINs, or the use of IRS to minimize the possibility of continued transmission.

Beyond Passive Case Detection: Active and Reactive Case Detection

Symptomatic individuals seeking care at health facilities due to a headache, fever, or other malaria-related symptoms are detected through passive case detection, the routine method within health systems. Passive case detection has limitations, however, especially in areas where health clinics are few and patients must travel far to access care. Passive case detection by design only detects symptomatic patients and overlooks asymptomatic individuals who, while not seeking medical attention, may continue to act as reservoirs of malaria parasites, especially within low prevalence areas. A surveillance system within a malaria elimination environment must be more sensitive than passive case detection affords. Hence, active case detection can act as another means to detect and reduce remaining parasite reservoirs.^{25,26} Active case detection can be performed through 'screen-and-treat' campaigns where teams periodically conduct house-to-house screening for malaria parasites dispensing antimalarials as necessary.^{14,27,28} These campaigns are no doubt effective; however, they are operationally and financially challenging to implement and require a high level of political support to maintain. As a result, screen-and-treat is perhaps best used as a short-term tactic to rapidly depress parasite prevalence to levels appropriate for focalized surveillance and intervention strategies. Such a screen-and-treat strategy is currently being mounted in Zambia (Appendix 1).

One such focal strategy has been termed 'reactive case detection' (RCD). RCD considers a passively detected case (reporting no recent travel and thus considered a locally acquired infection) as an index case and follows these up at the household level, screening and treating family members and neighbors within a defined radius. The index case is considered a proxy for other locally transmitted

infections. Several research programs and pilot projects in Zambia have focused on the implementation of RCD (Appendix 1), considering this a surveillance and response method used to achieve more effective malaria control as well as monitoring and supporting malaria elimination efforts.

Improving the Quality of Malaria Data

As countries progress towards malaria elimination and malaria control programs focus on stamping out remaining parasite reservoirs, high quality diagnostically confirmed malaria data are imperative.^{25,29} This will ensure that resources are not wasted by inadvertently following up a false positive. In Zambia, the National Malaria Control Centre (NMCC) has focused on improving their malaria data reporting practices through a program of intensified supervision and mentorship of Lusaka district health facilities which includes monthly reviews of clinic logbooks, intensive quality control of microscopy blood slide readings, and regular feedback and training. Through this program, clinicians are gaining increased trust in laboratory diagnostics and are reducing the number of clinical malaria diagnoses. This is helping clinicians to accept that malaria incidence is actually very low within the district. As a result, antimalarial drug prescriptions have at least halved since 2010, drawing the total number of prescriptions closer to total confirmed malaria cases. Increasing the quality of routine malaria surveillance data through a period of supervision and mentorship described here has been essential to the success of the RCD system (Appendix 1). Anecdotal information indicates that as clinic staff members become aware that the identification of a malaria case triggers a resource-intensive response, the requirement for diagnostically confirmed positives is reinforced and more strictly adhered to.

An Integrated Approach

Many health systems within malaria-endemic regions depend on cadres of community health workers (CHWs), or their equivalent, to extend health care directly into the community. CHWs are able to use RDTs for parasitological diagnosis and then provide immediate treatment for uncomplicated malaria.^{30–32} Utilizing CHWs who are both familiar within and respected by their communities greatly enhances community acceptance during responses (Appendix 1).³³ Continual support and training of CHW cadres in diagnostics, antimalarial provision, and record keeping will be essential as countries progress towards malaria elimination through enhanced surveillance.

Tools Needed to Advance Malaria Elimination

Diagnostic tools

The development of RDTs has transformed the ability to diagnose malaria in a field setting, where a cheap,

fast, and robust diagnosis can be performed by anyone having undergone basic training. However, RDTs have an Achilles heel — they are at best only able to detect 100 parasites per μL , making detection of low-density parasitemia unreliable,³⁴ and leaving a reservoir of disease only detectable by PCR.³⁵ In the context of countries transitioning to a pre-elimination agenda where transmission is very low, it is highly desirable that only confirmed cases are treated.³⁶ However, such wide scale testing is currently only practically possible using RDTs. As transmission intensity and malaria incidence fall, the development of protective immunity, e.g. in children, will likely be impaired.^{26,37} As a result, infections in these ‘naïve’ populations are more likely to be symptomatic.³⁷ Interestingly, in these low transmission settings, low-density parasitemias, i.e. below the RDT detection limit, are commonly identified.³⁸ These phenomena may not ultimately jeopardize the success of a campaign, but rather the time taken to achieve it. Nevertheless, efforts to extend the sensitivity of diagnostic tools for pre-elimination settings are drastically needed to empower surveillance systems to continue to identify malaria reservoirs.³⁹ This goal will most likely only be achieved if nucleic acid amplification techniques can be translated into the field setting. While loop-mediated isothermal amplification,⁴⁰ which provides PCR-like sensitivity without the requirement for a molecular laboratory, is the best available alternative, it simply cannot match the ease of use of an RDT kit.

Treatment for asymptomatic infections

A considerable proportion of an infected population can be asymptomatic,²⁸ although the size of this hidden disease reservoir varies dramatically according to transmission intensity.⁴¹ Asymptomatic individuals will not present to a health facility, unless for some other ailment, and therefore represent an intractable reservoir of disease unless actively detected. These long-term chronic infections provide the time required for asexual merozoites to undergo gametocytogenesis into gametocytes, the mosquito infective form. Gametocyte carriage, and subsequently the host infectivity rate, varies dramatically in different areas of the globe.⁴² Nevertheless, due to the limited number of mature gametocytes taken up in a blood meal, transmission from the human host to the mosquito vector represents a choke point in the lifecycle. While novel therapies for the symptom-causing asexual blood stages must continue to be developed,⁴³ the ability to incorporate a gametocytocidal agent into a combination therapy to block transmission will greatly further the elimination agenda. Currently the best combination consists of a standard course of ACT, active against immature

gametocytes, followed by a single dose of primaquine, active against mature gametocytes.⁴⁴ Unfortunately primaquine can cause severe hemolysis in individuals with a glucose-6-phosphate dehydrogenase deficiency, a common trait in sub-Saharan populations. Even combined, ACT+primaquine do not clear all gametocytes, therefore there is a serious need for developing a safe single-encounter radical cure (i.e. to clear all parasites in an individual),⁴⁵ especially in areas with high vectorial capacity where sub-microscopic gametocytemias result in transmission.⁴⁶

Challenges to elimination — efficacious tools

Given enough time and selection pressure, resistance to any compound will arise. It is therefore not surprising that, as the cornerstone of antimalarial therapies, the extensive usage of artemisinin has resulted in resistance.^{4,47} The threat that the development and dissemination of artemisinin-resistant parasites represent to the control or elimination of malaria cannot be underestimated. In response, the World Wide Antimalarial Resistance Network was established to monitor the situation and ensure that resistance is contained. Nevertheless, the development of resistance reinforces the need for continual research and development of new drugs and new drug combinations. Unfortunately the historically high-price of artemisinin has provided a criminal incentive to produce counterfeit/low-grade drugs, which are now increasingly being identified on the open market and thus threatening the quality of this life-saving drug.⁴⁸

Insecticide resistance also endangers the effectiveness of IRS and LLINs,⁴⁹ both of which currently rely heavily on the pyrethroid class of compounds that has a single mode of action. Resistance to this class is well documented and reinforces the need for the development of a range of novel insecticides, the development of resistance surveillance programs, and the implementation of insecticide rotation schemes to slow the development of resistance.⁵⁰

The seemingly inevitable rise of drug and insecticide resistance, the long development pipeline, and the paucity of immediate replacement compounds suggests that it is time to re-assess and strengthen the use of all other currently available methods or those that may become available in the near future, e.g. intermittent preventive therapy in infants,⁵¹ larviciding,⁵² environmental management, and malaria vaccines.⁵³

Mobile phones support malaria elimination

The adoption of mobile phone communications throughout the developing world has occurred at breakneck speed. Mobile operators have invested heavily in infrastructure to transform network coverage in

Africa from 10% at the turn of the century to an estimated 70–85% in 2010.^{54,55} While handset ownership lags behind coverage, it is clear that mobile phones are becoming a ubiquitous feature in even the most rural setting. In this dynamically changing environment, where underlying technologies develop and mature to provide additional functionality, mobile phones offer the perfect tool for establishing high quality surveillance systems for monitoring malaria and identifying reservoirs of symptomatic infections more rapidly.

Multiple RCD efforts in Zambia are currently utilizing mobile phones (Appendix 1). A simple SMS-based system was developed and successfully deployed to support data collection of the RCD system implemented in and around Macha.⁵⁶ Rural health workers were trained to send a coded text message reporting the number of RDTs performed and number positive, on a weekly basis. This timely reporting enabled relatively precise temporal mapping of cases. While this system relies on manual compilation of SMS data into a spreadsheet, it firmly establishes the potential for mobile phones to be used for timely reporting.

Based on the experience gained in the research setting, the Zambia NMCC and partners recently developed a scalable mobile reporting platform to improve malaria surveillance which is based on the open-source District Health Information System (DHIS2; www.dhis2.org). Taking advantage of the locally competitive mobile telephony market, data (as opposed to SMS) for 17 key malaria surveillance indicators are transmitted directly from the clinic, and are immediately available through the system for decision making.⁵⁷ A key feature is the mobile reporting module, which introduces field-based forms for malaria data collection on any java-enabled phone. Currently in Zambia, around 500 health centers have been equipped with a phone and weekly reporting of malaria indicators has been under way since early 2011. This system is now being extended to support CHWs implementing RCD in Southern Province. All levels of the health system from provincial to district to health center can access malaria data pertinent to their situation to strengthen local ownership, more rapidly respond to epidemiological changes, and reduce reporting errors and repetitive tasks associated with reporting (e.g. data aggregation). Furthermore, new forms and indicators can easily be added to the mobile phone client, making this tool capable of reporting on a wealth of health and development indicators.

Whichever mobile communication system is implemented, information must be accessible at all levels of the health system hierarchy. Where there are bottlenecks or barriers to access, data must be actively

disseminated. For example, sending regular SMS messages with simple case management information to health workers has been shown to have an impressive effect on adherence to treatment guidelines.⁵⁸ As countries target malaria elimination, either nationally or locally, mobile phone technology is likely to play a key role.

The bigger picture: putting it all together

Environments and people are heterogeneous; hence malaria burden tends to vary across regions. As such, it may be necessary to apply different malaria control and elimination strategies within a country during different times and in different areas depending upon the environment, malaria burden, and seasonal effects.²⁹ For example, screen-and-treat campaigns implemented alone in an area with low vector capacity may sustainably reduce the incidence of parasitemia to a level where it is feasible to respond to individual cases through RCD. In contrast, where vector capacity/transmission potential is very high, the benefits of screen-and-treat campaigns may not be sustained, unless augmented with other interventions to prevent resurgence. In either case, the risk of importation of malaria through the movement of infected people into the elimination zone means that surveillance systems must always be alert and primed to respond to minimize the risk of outbreaks within an elimination area.^{11,12}

In any environment, regardless of burden intensity, a robust reporting, surveillance, and response system operated by well-trained health workers utilizing quality diagnostics and efficacious drugs will enable the identification, treatment, and mapping of malaria cases. Ultimately, this will be key to adopting an appropriate strategy for each malaria transmission zone,²⁵ and its subsequent success or failure.

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Appendix 1: Surveillance and focal interventions in Zambia

The Zambia NMCC has identified a goal of five malaria free zones by 2015.²⁰ To achieve this goal, the Ministry of Health (MOH) with support from partners, and funding from Malaria Control and Evaluation Partnership in Africa, are rolling out a multi-faceted system termed Steps 1–2–3. This step-wise strategy begins with Step 1, the malaria rapid reporting system, to provide timely data through the submission of weekly reports by health facility workers to a central server via mobile phones.⁵⁷ These data are used to inform whether to proceed with the adoption of Step 2 or Step 3 interventions to further reduce the malaria burden. Step 2 refers to a

short-term screen-and-treat campaign that is applied during the dry season to quickly depress malaria transmission to a level suitable for Step 3. In contrast, Step 3 is applied in very low prevalence areas by improving the malaria surveillance and response system to include the activation of focalized interventions.

Step 3, which is a form of reactive case detection⁵⁹ has been informed by research conducted in a rural region of Southern Province, Zambia, led by the Malaria Institute at Macha.⁵⁶ This study confirmed that asymptomatic malaria parasite carriers cluster around symptomatic malaria cases,³⁵ thus providing a method to focus malaria control efforts to areas of localized transmission. The Zambia MOH and partners are now integrating Step 3 into the MOH approach in areas of low parasitemia prevalence. To date, Lusaka District, the urban center of Zambia, has applied this approach in 10 clinic catchment areas with support from PMI. A response team investigates malaria index cases confirmed at the clinics and screens and treats their family members and neighbors. Through this system, low levels of malaria transmission have been documented, significant health system improvements have been made, and an increase in surveillance sensitivity and specificity has improved the capacity to monitor progress towards malaria elimination and to respond to focal areas of malaria transmission quickly and effectively.

Step 3 is also being rolled out in rural areas of Zambia's Southern Province through CHWs who form a network of satellite health posts surrounding a single rural health clinic. These individuals respond to cases passively detected both at the clinic and during their routine testing of symptomatic community members, providing antimalarials as necessary. Aggregated surveillance data are transmitted via cell phones to detect hot spots of transmission as well as to monitor the progress towards malaria elimination. Steps 1–2–3 are being methodically rolled out in areas of moderate and low malaria transmission in Zambia with the aim of enhancing reporting and surveillance frameworks, informing intervention decisions, and monitoring the malaria burden with a view to malaria elimination in target areas by 2015.

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